Enantioselective recognition of chiral carboxylic anions by a ruthenacyclic receptor

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A ruthenacyclic complex comprising the Ru^+–NH unit, chiral at the metal centre, was shown to complex and discriminate two enantiomeric carboxylic substrates. Binding was highlighted by spectra changes in ^1H NMR and IR spectroscopy. Due to the configurationally labile metal centre, the two (*R*) and (*S*) enantiomeric substrates are bound, but each one specifically to one stereoisomer of the receptor.

Introduction

Molecular recognition is the key step in a wide range of controlled biological and chemical processes. Several strategies have been developed towards the enantioseparation and stereoselective synthesis of chiral drugs, agrochemicals and fragrances.[1] The design of selective receptors and catalysts has become a central challenge in molecular chemistry.[2]

Anions are ubiquitous in the natural world and play numerous roles in biological and chemical features.[3] Among them, chiral carboxylic anions represent interesting subjects in enantiorecognition because of their important presence in enzymes as substrates and cofactors, antibodies and metabolic intermediates.[4]

A possibility in the design of an agent able to complex a carboxylic acid is the incorporation of a metal centre, with which the anion may form a coordination bond. A rationally designed compound based on a tetradentate cobalt (III) complex has been shown to bind amino acids with high and predictable stereoselectivity.[5] Steroids bearing guanidinium functionalities are known to selectively extract *N*-acetyl α-amino acids.[6] Macrocyclic systems based on tetrapyrrole[7] or containing urea functionalities[8] also perform enantioselective recognition towards carboxylic anions.

An approach for the design of an anion receptor could be the combination of the structural and functional properties of a metal centre with the recognition capabilities of a hydrogen bonding group. Such a receptor was synthesized in our laboratory following that line. It combines a cobalt (III) centre with an ammonium unit.[9] Our aim was then to develop a chiral version of this receptor. Herein is reported a carboxylic anion enantiorecognition study with the chiral ruthenacyclic receptor **1** (Scheme 1).[10]

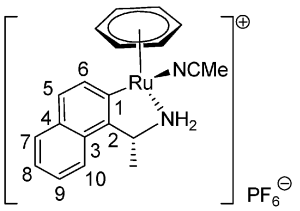
Results and discussion

The key compound in this study is the tetrahedral ruthenacyclic complex **1** built up from a chiral primary amine. In this compound, the chirality at the ruthenium centre is induced by the chirality of the cyclometalating unit. After cyclometalation the organometallic complexes exist as a mixture of two diastereomers. The highest diastereomeric excess (de = 97% at RT in CD_3CN) was found with the ligand (*R*)-1-(1-naphtylethylamine).

1-Methoxy-1-trifluoromethyl-phenyl acetic acid, namely Mosher's acid, was selected as a guest.[11] The binding properties of **1** were investigated in three different solvents: methanol as a polar and protic solvent, acetonitrile as polarisable solvent and dichloromethane as weakly polar solvent. A 1/1 mixture of the receptor **1** (10 mM) and the corresponding (*R*) or (*S*) anionic guests (as their NMe_4^+ salts) were dissolved in deuterated solvents. As shown in Fig. 1, upon the addition of the substrate, dramatic changes in the ^1H NMR spectrum were observed. The spectra superposition shows the decrease of the free receptor signals and the appearance of a new set of shifted signals related to obviously new species. The new signals were attributed to the receptor–substrate complexes. The simultaneous observation of the proton signals for the free and bound receptor indicates slow exchange between the two species. Free acetonitrile is discarded in the solution, allowing an interpretation in terms of an exchange phenomenon between the carboxylic and acetonitrile ligands.

Formation of a complex species between the guest and its host was confirmed by infrared spectroscopy. In Fig. 2, the different spectra of the substrate, receptor and 1/1 mixture of the two substrates are seen.

The vibration associated with the carboxylate function is slightly shifted from 1640 to 1632 cm^{-1}. The stretching vibrations at 3337 and 3292 cm^{-1}, due to the amino function of **1**, are strongly affected by the addition of the substrate. This is interpreted as an interaction between the NH of the receptor



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Scheme 1

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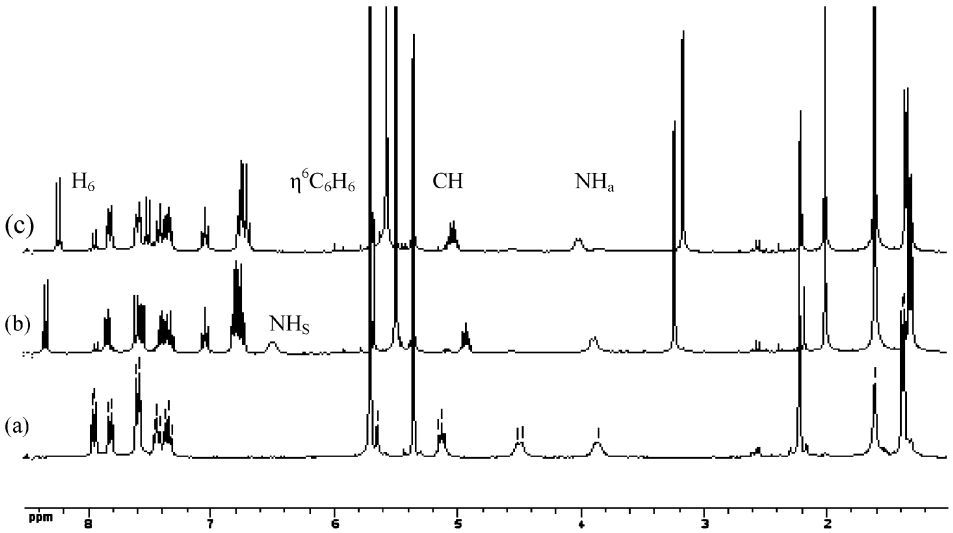

Fig. 1 ^{1}H NMR spectra: free receptor and receptor–substrate complexes in CD_2Cl_2. From bottom to top: (a) free receptor **1**; (b) 1/1 mixture of the receptor and the (*R*) substrate; (c) 1/1 mixture of the receptor and the (*S*) substrate.

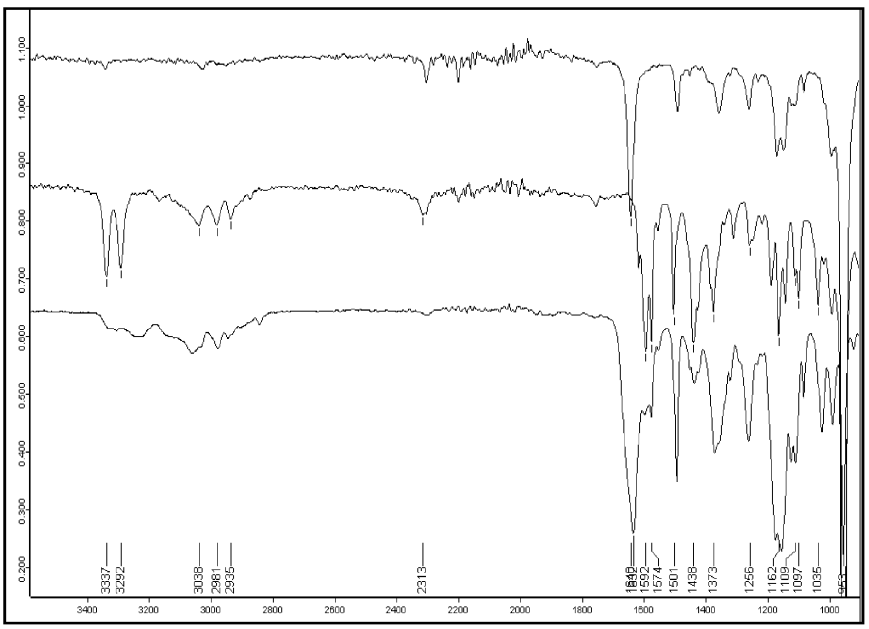

Fig. 2 Infrared spectra. From top to bottom: (a) substrate as its NMe_4^+ salt; (b) free receptor **1**; (c) 1/1 mixture of the receptor and substrate.

and the carboxylic function, leading the formation of the receptor–substrate complex.

Under the reasonable hypothesis of one-to-one complex formation, the equation in the direction of dissociation and the resulting dissociation constant K[12] can be expressed as:

$$\mathbf{1},(R)\text{-}CO_2^- + NCMe \rightleftharpoons \mathbf{1}\text{-}NCMe + (R)\text{-}CO_2^-$$

$$K = \frac{[\mathbf{1}\text{-}NCMe](R)\text{-}CO_2]}{[\mathbf{1},(R)\text{-}CO_2][NCMe]}$$

The respective signal integrals of the new complex and the remaining free receptor displayed in Fig. 1 have been extracted for the calculation of the complexed fraction (see Table 1). The peaks corresponding to the H_6 proton, the $\eta^6C_6H_6$ unit and the acetonitrile ligand were chosen for this task. The percentage of the bound (*R*) and (*S*) guests remained nearly the same in CD_3CN and CD_3OD (no selectivity was displayed in these solvents). On the contrary, in CD_2Cl_2, receptor **1** exhibited a discriminating ability towards the (*R*) substrate. The percentage of the bound fraction of the (*R*) substrate (86 ± 1%) was greater than that of the (*S*) substrate (77 ± 2%), leading to a selectivity of 3.5 ± 0.5. The exchange constant calculated for the best recognized substrate was 0.026.

Furthermore, an extraction was carried out between an aqueous (D_2O) and an organic phase (CD_2Cl_2). Aqueous solutions of the (*R*) and (*S*) substrates (1 mL, 10 mM) were added to **1** in CD_2Cl_2 (1 mL, 10 mM) and stirred. NMR revealed the presence of the new complex in the organic phase,

together with remaining free receptor. In the aqueous phase, the NMe_4^+ cation was found in excess with respect to the substrate, the excess corresponding to the PF_6^- anion extracted from the organic phase. The equation and corresponding extraction constant K can be expressed as follows:

$$[\mathbf{1},(R)\text{-}CO_2^-]_{org} + [NCME]_{org} + [NMe_4^+,PF^-{}_6]_{aq} \rightleftharpoons [\mathbf{1}\text{-}NCMe, PF_6^-]_{org} + [NMe_4^+,(R)\text{-}CO_2^-]_{aq}$$

$$K = \frac{[\mathbf{1}, \text{-}NCMe, PF_6]_{org}[NMe_4^+, (R)\text{-}CO_2]_{aq}}{[\mathbf{1}, (R)\text{-}CO_2]_{org}[NCMe]_{org}[NMe_4^+, PF_6]_{aq}}$$

As a result, the (*R*) substrate (76 ± 2%) remained better recognised by the receptor than the (*S*) substrate (59 ± 2%). The factor of selectivity (6 ± 1) was enhanced in this extraction experiment.

In Table 1, the chemical shift changes ($\Delta\delta$ in ppm) for the selected H_6, $\eta^6C_6H_6$ and NH signals are given. The H_6 and the NH protons exhibit downfield shifts, while η^6-C_6H_6 unit is displaced to up-field shifts in all the solvents used. As a whole, it can be noticed that the chemical shifts changes for the (*R*) are ever greater than those for the (*S*) substrate, except for the signal of the NH_a proton. This tendency may be related to better interaction of the (*R*) over the (*S*) substrate. The chemical shift changes for NH_s are the highest measured, especially in CD_2Cl_2 (2 ppm). Hence, NH_s is certainly involved in the recognition of the substrate by the establishment of a hydrogen bond with the carboxylate moiety.

The signals of the substrate were not chosen for the calculation of the complexed fraction because of overlap with some receptor signals. However, changes occurred within the substrate after complexation. The proton signals of the phenyl group of the substrates were shifted downfield. Moreover, the phenyl pattern of the free substrate changed into a better-resolved triplet–doublet–triplet pattern. The signal of the methoxy function was also shifted downfield but slightly more for the (*S*), 0.41 ppm, than for the (*R*), 0.35 ppm, guest.

As the existence of a receptor–substrate complex and the selectivity displayed by the receptor are well established, the question of the complexes structure still remained. The receptor is a mixture of configurationally-labile at the metal centre diastereomers.[13] Its composition depends on the nature of the ligand (acetonitrile, methanol, phosphane, hydride).[14] In order to gain further insight into the nature of the complex, we studied the binding of the acetate anion by NMR (Fig. 3) and infrared.

The spectra superposition shows the disappearance of the free receptor signals and the appearance of a set of new shifted signals related to the receptor–substrate complexes. The H_6 proton appears as two downfield-shifted signals while the two η^6-C_6H_6 signals are displaced up-field. The proton of the acetate substrate was also shifted up-field. These data were interpreted as a mixture of two diastereomeric at the ruthenium centre receptor–acetate complexes of de = 76%, an excess different from that in the starting receptor. This interpretation was related to an exposition of the two Mosher anions to two different, but interchangeable, environments originating from the configurational conversion of the metal centre, thus leading to (*R*) and (*S*) substrate–receptor complexes of respective (RS_{Ru}), (*R*) and (RR_{Ru}), (*S*) stereochemistry. Without any change, the major diastereomeric receptor complexes the (*R*) substrate. Binding of (*S*) requires a configuration change at the metal centre to achieve a better fit with the substrate.

Two mean structures may be proposed for these two complexes under the statement that rotations scramble these structures. (i) The mode of interaction of the carboxylic unit has been established by X-ray diffraction. The crystallographic structure of the Cp*Ir ($OCOCH_3$) [κ^2-(*N*,*C*)-H_2NCPh_2-2-C_6H_4] species, **2**, an acetate complex of the tetrahedral irida-cycle, has been established independently.[15] In that structure, one oxygen atom is linked to the metal through a coordination bond and the other interacts with a hydrogen atom from the amino function (OH distance 2.278 Å, OHN angle 124.72°). NMR further evidences that upon interaction, a significant down-field shift of one of the NH signals of the amino functionality is observed. (ii) The chemical shift changes observed in the same direction for the benzene ligand in **1** (see Table 1) and the phenyl group of the anionic substrates are interpreted as resulting from a CH–π interaction.[16] To visualize this interaction, the following mean structures are proposed in Fig. 4.

Conclusion

A ruthenacyclic complex comprising the Ru^+–NH unit, which is chiral at the metal centre, was shown to complex and discriminate two enantiomeric carboxylate substrates. Binding was highlighted by spectral changes in proton NMR and IR

Table 1 Selected chemical shift changes in ppm. Changes measured in the 1/1 receptor–substrate mixture with respect to the free receptor (10 mM). Percentage of bound substrates and errors were estimated from onset integrals

	$\Delta\delta$ (H_6)	$\Delta\delta$ (η^6-C_6H_6)	$\Delta\delta$ (NH_s)	$\Delta\delta$ (NH_a)	Percentage complex	Selectivity
CD_3CN						
R	0.35	−0.17	1.07	0.20	56 ± 2	1
S	0.23	−0.12	0.53	0.20	56 ± 2	
CD_3OD						
R	0.39	−0.17	—	—	56 ± 1	1
S	0.30	−0.12	—	—	58 ± 1	
CD_2Cl_2						
R	0.41	−0.19	2.00	0.03	86 ± 1	3.5 ± 0.5
S	0.30	−0.12	1.10	0.15	77 ± 2	
CD_2Cl_2/D_2O						
R	0.40	−0.19	2.00	0.03	76 ± 2	6 ± 1
S	0.29	−0.13	1.10	0.15	59 ± 2	

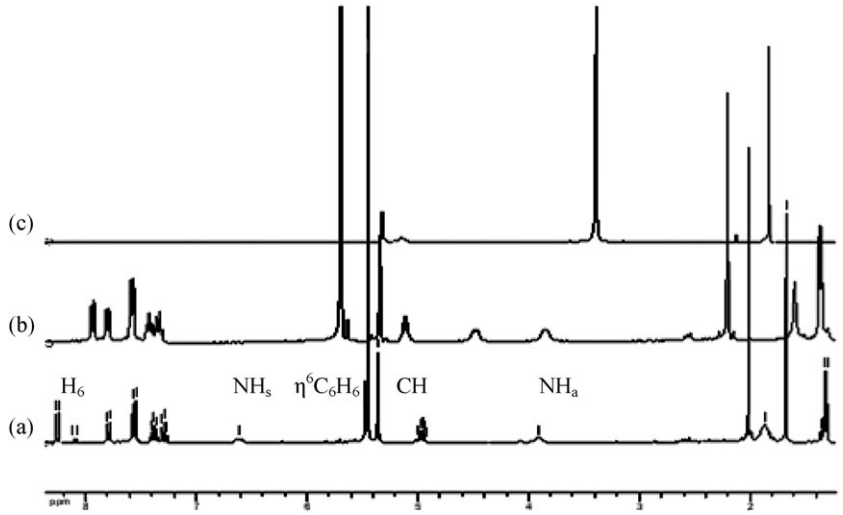

Fig. 3 ^{1}H NMR spectra: mixture (10 mM) of receptor and substrate in CD_2Cl_2. From the bottom to top: (a) 1/1 mixture of the receptor and acetate; (b) free receptor; (c) free acetate anion.

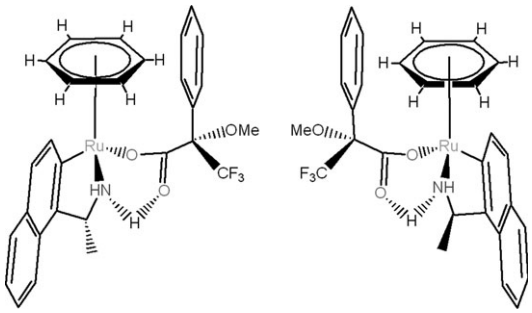

Fig. 4 (RS_{Ru}), (R) (right) and (RR_{Ru}), (S) (left) substrate–receptor structures.

spectroscopy. The free and bound species are in slow exchange. The measured selectivity factor of 6 may be compared with results obtained with rather different systems, such chiral guanidine or urea[17] receptors conjugated with a steroid skeleton. Due to the configurationally-labile metal centre, the two (R) and (S) substrates are bound, but each specifically to one stereoisomer of the receptor.

Experimental section

Deuterated solvents were obtained from Euriso-top®. (S) and (R) Mosher's acids and $NMe_4^+OH^-$ were purchased from Aldrich. NMe_4^+ salts of the Mosher's acids were prepared by mixing equimolar amounts of Mosher's acids and $NMe_4^+OH^-$ in methanol. The solutions were dried under vacuum and used without any other purification. ^{1}H NMR spectra were recorded at 300.13 MHz on an AC-300 Bruker spectrometer and $^{13}C\{^1H\}$ NMR spectrum on ARX-500. IR spectra were obtained on an ALPHA FT-IR spectrometer. ES-MS spectra and elemental analyses were carried out at the Institut de Chimie, Strasbourg and Service central d'analyse du CNRS, Vernaison.

1 ≡ [(η^6-C_6H_6)Ru($C_{10}H_6$-2-(R)-$CHCH_3NH_2$)($NCCH_3$)]PF_6

1 was available from our laboratory. HRMS (ES, m/z): Calc. for $C_{18}H_{18}N^{102}Ru$: 350.0482; found: 350.0783. Anal. calc. for $C_{20}H_{21}F_6N_2PRu{\cdot}0.25CH_3CN$: C 45.12, H 4.02, N 5.78; found C 45.55, H 4.28, N 5.50.

^{1}H NMR (300 MHz, CD_2Cl_2, 300 K):

Major isomer (97%), δ 7.92 (d, 1H, H_6, $^3J_{HH}$ = 8.4 Hz), 7.79 (d, 1H, H_{10}, $^3J_{HH}$ = 8.1 Hz), 7.56 (d, 2H, H_7, H_5, $^3J_{HH}$ = 8.1 Hz), 7.41 (ddd, 1H, H_8, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 6.9 Hz, $^4J_{HH}$ = 1.5 Hz), 7.31 (ddd, 1H, H_9, $^3J_{HH}$ = 8.1 Hz, $^3J_{HH}$ = 6.9 Hz, $^4J_{HH}$ = 1.2 Hz), 5.68 (s, 6H, η^6-C_6H_6), 5.09 (qui, 1H, C*H*CH_3, $^3J_{HH}$ = 6.3 Hz), 4.48 (d, 1H, NH_s, $^2J_{HH}$ = 11 Hz), 3.81 (br, 1H, NH_a), 1.34 (d, 3H, CH_3, $^3J_{HH}$ = 6.3 Hz).

Minor isomer (3%), 8.09 (d, 1H, H_6, $^3J_{HH}$ = 8.4 Hz), 5.61 (s, 6H, η^6-C_6H_6), 2.23 (s, 3H, CH_3CN), 1.50 (d, 3H, CH_3, $^3J_{HH}$ = 6.9 Hz).

$^{13}C\{^1H\}$ NMR (125 MHz, CD_3CN, 273 K): δ 164.9 (C1), 146.7 (C2), 139.2 (C6), 132.2 (C4), 129.1 (C5), 128.8 (C3), 126.4 (C8/9), 124.0 (C7/10), 123.8 (C7/10), 118.2 (CN), 87.3 (C_6H_6), 59.3 (CH), 21.5 (CH_3).

[(η^6-C_6H_6)Ru($C_{10}H_6$-2-(R)-$CHCH_3NH_2$)](R)-(Ph, OMe, CF_3,CCO_2^-)

^{1}H NMR (300 MHz, CD_2Cl_2, 300 K): δ 8.33 (d, $^3J_{HH}$ = 8.4 Hz, H_6 b), 7.92 (d, $^3J_{HH}$ = 8.4 Hz, H_6 f), 5.68 (s, η^6-C_6H_6 f), 5.49 (s, η^6-C_6H_6 b), 6.48 (d, NH_s b), 3.84 (d, NH_a b); b = bound, f = free.

[(η^6-C_6H_6)Ru($C_{10}H_6$-2-(S)-$CHCH_3NH_2$)](S)-(Ph, OMe, CF_3,CCO_2^-)

^{1}H NMR (300 MHz, CD_2Cl_2, 300 K): δ 8.22 (d, $^3J_{HH}$ = 8.4 Hz, H_6 b), 7.92 (d, $^3J_{HH}$ = 8.4 Hz, H_6 f), 5.68 (s, η^6-C_6H_6 f), 5.56 (s, η^6-C_6H_6 b), 5.58 (d, NH_s b), 3.96 (d, NH_a b); b = bound, f = free.

[(η^6-C_6H_6)Ru($C_{10}H_6$-2-(R)-$CHCH_3NH_2$)], CH_3CO_2

^{1}H NMR (300 MHz, CD_2Cl_2, 300 K): δ 8.26 (d, $^3J_{HH}$ = 8.4 Hz, H_6 M), 8.10 (d, $^3J_{HH}$ = 8.4 Hz, H_6 m), 7.79 (d, $^3J_{HH}$ = 8.1 Hz, H_{10}), 7.40 (t, $^3J_{HH}$ = 8.1 Hz), 7.30 (t, $^3J_{HH}$ = 8.4 Hz), 6.62 (ls, NH), 5.47 (s, η^6-C_6H_6 m), 5.44 (s, η^6-C_6H_6 M), 5.09 (m, C*H*CH_3),

3.91 (ls, NH), 1.67 (s, CH_3CO_2), 1.35 (d, $^3J_{HH}$ = 6.3 Hz, CH_3 m), 1.31 (d, $^3J_{HH}$ = 6.3 Hz, CH_3 M); M = major diastereomer, m = minor diastereomer.

Calculation of the selectivity factors

One phase experiments.

$$\mathbf{1},(R)\text{-}CO_2^- + NCMe \rightleftharpoons \mathbf{1}\text{-}NCMe + (R)\text{-}CO_2^-$$

$$K = \frac{[\mathbf{1}\text{-}NCMe](R)\text{-}CO_2]}{[\mathbf{1},(R)\text{-}CO_2][NCMe]}$$

$$K(R) = 14 \times 14/86 \times 86 = 2.6 \times 10^{-2}$$
$$K(S) = 23 \times 23/77 \times 77 = 8.9 \times 10^{-2}$$
$$\alpha = \{K(R)/K(S)\}^{-1} = 3.4$$

Two phase experiments.

$$[\mathbf{1},(R)\text{-}CO_2^-]_{org} + [NCME]_{org} + [NMe_4^+,PF^-{}_6]_{aq} \rightleftharpoons [\mathbf{1}\text{-}NCMe,PF_6^-]_{org} + [NMe_4^+,(R)\text{-}CO_2^-]_{aq}$$

$$K = \frac{[\mathbf{1},\text{-}NCMe,PF_6]_{org}[NMe_4^+,(R)\text{-}CO_2]_{aq}}{[\mathbf{1},(R)\text{-}CO_2]_{org}[NCMe]_{org}[NMe_4^+,PF_6]_{aq}}$$

$$K(R) = 24 \times 24/76 \times (76 \times 10^{-4}) \times 76 = 13$$
$$K(S) = 41 \times 41/59 \times (59 \times 10^{-4}) \times 59 = 82$$
$$\alpha = \{K(R)/K(S)\}^{-1} = 6.3$$

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